REMARKS

In responding to the Office Action, Applicant conducted a telephone interview with Examiner Winkler on January 20, 2004. Applicant thanks the Examiner for the time generously extended for this interview. During this interview, the pending rejection and amendments to the claims were discussed. Applicants presented arguments for patentability that the Examiner indicated may render the present application allowable over Crance et al. Travaux 1999 ("Crance") and U.S. Patent No. 6,387,365 ("Albrecht"). These arguments are presented below.

Applicant has amended claim 5, as discussed during the interview, to include methods for preventing or treating meningitis, encephalitis, or meningo-encephalitis caused by West Nile virus infections by administering an effective amount of interferon alpha-2b. Support for this amendment is found in the specification, for example, at page 4, lines 23-28. By this amendment, Applicant has also added claims 17-24, which are directed to methods of treating West Nile virus infections by administering interferon alpha-2b subcutaneously or intravenously to humans. Support for claims 17-24 is found in the specification, for example, at page 4, lines 10-15, and page 8, lines 7-8, and claims 5-9 as originally filed. Applicant submits that no new matter is added by this amendment. Entry of the amendment, and reconsideration of the application as amended is respectfully requested.

Rejection Under 35 U.S.C. § 103(a)

The Examiner rejects claims 5-9 under 35 U.S.C. §103(a) as allegedly being unpatentable over Crance in view of Albrecht. Applicant respectfully traverses this rejection.

The Examiner asserts that Crance discloses the effect in cell culture of interferon-alpha 2b on different flaviviruses including West Nile. The Examiner concedes that Crance does not disclose administering interferon alpha-2b to a patient. However, the Examiner uses Albrecht for teaching that interferon alpha-2b can be used at doses of 3 to

10 million IU for treating patients that have chronic hepatitis C viral infections. Although the Examiner concedes that Albrecht does not teach treating West Nile virus infections using interferon alpha-2b, nevertheless, the Examiner concludes that one of ordinary skill in the art would have "a high expectation of success" in using interferon alpha-2b to treat West Nile virus infections in view of Crance's *in vitro* cell culture results and Albrecht's teachings of using interferon to treat hepatitis C infections. (Office Action, Page 4)

Applicant respectfully disagrees with the Examiner's position. To establish a *prima facie* case of obviousness, all of the claim elements must be taught or suggested by the prior art. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir.1991). The claims have been amended to include that the interferon alpha-2b is used to prevent or treat meningitis, encephalitis, or meningo-encephalitis caused by West Nile virus infection.

Although Crance discloses interferon alpha-2b activity on West Nile virus in select cell lines, Crance does not disclose, teach or suggest using interferon alpha-2b for the prevention or treatment meningitis, encephalitis, or meningo-encephalitis caused by West Nile virus infections. Applicant respectfully submits that West Nile virus meningitis, encephalitis, or meningo-encephalitis is a central nervous system (CNS) infection that can affect, for example, the brain or spinal cord. Crance does not disclose, teach or suggest that interferon alpha-2b could be used to treat infections in the CNS. Applicant directs the Examiner's attention to the enclosed references, *http://www.cancercare.on.ca* and *http://www.vu-wien.ac.at/i123/allgemeininfo.html* (website visited February 17, 2003), and Smith *et al.* Clin Pharmacol Ther. 1985 Jan;37(1):85-8 (abstract), discussing that interferon-alpha 2b has little or no penetration across the blood-brain barrier into the CNS. Thus, one of ordinary skill in the art would not expect interferon alpha-2b to be useful in treating a CNS infection associated with the West Nile virus. Applicant respectfully directs the Examiner's attention to Marfin and Gubler, West Nile Encephalitis: An Emerging Disease in the United States, *Clinical Infectious Diseases,* 33:1713-9 (2001), published after the filing of this application,

where experts in the field describe that there is no effective therapy for treatment of West Nile virus (*see* Marfin at page 1717). Thus, before the presently claimed invention, one of ordinary skill in the art would not have any expectation of success in preventing or treating West Nile by administering interferon alpha-2b, because experts concluded that there was no effective treatment for West Nile virus infections.

Albrecht is cited by the Examiner for teaching that interferon alpha-2b can be used at doses of 3 to 10 million IU for the treatment of chronic hepatitis C viral infections —in the same family as the West Nile virus. However, Applicant respectfully submits that hepatitis C infections are localized viral infections of the liver that can result in cirrhosis of the liver, decompensated liver disease and/or hepatocellular carcinoma (see Albrecht col. 1, lines 4-8). These liver diseases are not the same as CNS infections involving the brain and/or spinal cord. As stated above, interferon alpha-2b does not penetrate the CNS to any great extent, interferon alpha-2b levels in the CNS are low, thus the *in vitro* data of Crance and the dosing regimen disclosed in Albrecht can not simply be applied to CNS infections such as meningitis, encephalitis, or meningo-encephalitis caused by the West Nile virus, because the site of the infection is different, and the penetration of interferon alpha-2b in the CNS is low. Accordingly, upon reading Crance and Albrecht alone or in combination, one of ordinary skill in the art would not obtain the present invention as claimed, nor would it be obvious to one of ordinary skill in the art. Even if one of ordinary skill in the art were to combine Crance and Albrecht, one may expect success at treating liver infections, not CNS infection. Accordingly, Applicants respectfully submit that the rejection under 35 U.S.C. §103(a) is improper, and Applicant requests withdrawal of this rejection.

Conclusion

In view of the foregoing amendments, and the remarks set forth above, reconsideration and allowance are respectfully solicited.

Enclosed is the fee authorization for a one-month extension of time. No additional fee is believed to be due with respect to the filing of this amendment. If any additional fees are due, or an overpayment has been made, please charge, or credit, our Deposit Account No. 11-0171 for such sum.

If the Examiner has any questions regarding the present application, the Examiner is cordially invited to contact Applicant's attorney at the telephone number provided below.

Respectfully submitted,

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Distribution of alpha interferon in serum and cerebrospinal fluid after systemic administration

After intravenous infusion of recombinant leukocyte interferon (rIFN-αA) to four subjects with an indwelling reservoir, serial serum and cerebrospinal fluid samples were taken over 48 hr and were analyzed for interferon by an enzyme immunoassay method (ELISA). On separate occasions, 18 and 50 × 10^6 of rIFN-αA were infused over 10 min. Maximum serum concentrations of rIFN-αA ranged from 6720 to 11,000 pg/ml and from 32,900 to 43,400 pg/ml after the 18 and 50 × 10^6 U doses. There was no measurable concentration of rIFN-αA in the cerebrospinal fluid of subjects who received 18 × 10^6 U doses. In three of four subjects who received 50 × 10^6 U rIFN-αA, concentrations ranged from 17 to 70 pg/ml that were measurable no earlier than 1 hr after the start of the infusion and that in two cases were measurable throughout 24 hr. (CLIN PHARMACOL THER 37:85-88, 1985.)

Richard A. Smith, M.D., Forbes Norris, M.D., Darryl Palmer, Leon Bernhardt, M.D., and Robert J. Wills, Ph.D. *San Diego and San Francisco, Calif., Boston, Mass., and Nutley, N. J.*

Interferons are potent immunomodulatory, antiviral, and cytostatic substances that may have application in diseases of the nervous system.[6-10] Because of the effect of the blood-brain barrier, the route of administration of interferon may be an important variable in the treatment of neurologic disorders.[10] After systemically administering partially purified α-interferon to stumptailed monkeys, Habif et al.[4] found the serum/cerebrospinal fluid (CSF) concentrations ratio to be 30:1. In a similar study, Riccardi et al.[9] found a serum/CSF ratio of approximately 2000:1 after systemic administration of recombinant α-interferon (rIFN-αA) to Rhesus monkeys. Parallel data in man would be important in the treatment of neurologic diseases with interferons; furthermore, such data might contribute to the interpretation of nervous system side effects recently reported in patients treated with interferon.[8,12] Accordingly, we investigated the distribution of rIFN-αA in serum and CSF of patients after systemic administration.

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METHODS

Our subjects were four patients with amyotrophic lateral sclerosis who were to be treated later with intraventricular interferon. Each patient had an Ommaya (American Hospital Supply) reservoir that had been surgically placed approximately 3 wk before dosing with human rIFN-αA. The rIFN-αA was produced by Hoffmann-La Roche Inc by recombinant deoxyribonucleic acid methods. On the morning of each injection, a venous catheter was inserted in each arm. Blood samples were drawn from one arm and were centrifuged to obtain serum. The rINF-αA was infused intravenously in the other arm over 10 min. After rINF-αA injection, blood (5 ml) and CSF (3 ml) samples were collected serially over 48 hr. CSF samples were obtained by tap of the Ommaya reservoir under sterile conditions. Plasma and CSF samples were rapidly frozen immediately after collection and stored at −70°. The subject's clinical status was evaluated for 48 hr after dosing, and side effects commonly associated with interferon were rated for severity. The first infusion consisted of an 18 × 10^6 U dose of rIFN-αA. Approximately 2 wk after the first experiment, the same subjects were restudied with a dose of 50 × 10^6 U rIFN-αA.

Human rIFN-αA was measured by an enzyme-immunoassay method (ELISA) by means of a solid-phase sandwich principle, i.e., two monoclonal antibodies

Table I. Titers in serum and CSF after intravenous infusion of rIFN-αA

	rIFN-αA dose			
	18 × 10⁶ U		50 × 10⁶ U	
Time	Serum (pg/ml)	Ventricular CSF (pg/ml)	Serum (pg/ml)	Ventricular CSF (pg/ml)
0	<23*	<15	<16	<15
5 min	5440 ± 775	—	21,000 ± 940	—
10 min	9340 ± 945	—	38,000 ± 2150	—
15 min	5260 ± 1050	—	35,100 ± 3290	—
30 min	2570 ± 1050	<15	18,900 ± 2240	<15
60 min	1150 ± 400	<15	9990 ± 870	50
2 hr	430 ± 190	<15	3210 ± 250	45
4 hr	170 ± 60	<15	595 ± 155	35
8 hr	55 ± 35	<15	165 ± 60	20
12 hr	35 ± 20	<15	95 ± 60	15
24 hr	†	<15	30 ± 20	20
48 hr	†	<15	†	<15

Data are $\overline{X} \pm$ SE.
*One subject had elevated baseline serum rIFN-αA titers.
†An average was not computed when rIFN-αA levels were undetectable in one or more subjects.

Table II. Pharmacokinetic parameters

Subject	C_{max}* (pg/ml)	$AUC_{0-\infty}$ (pg · ml/hr)	$t_{1/2}$ (hr)	Total body clearance (ml/min)	Serum C_{max}/CSF C_{max} ratio
18 × 10⁶ dose					
M. P.	9230	2770	1.2	650	
E. F.	10,400	6750	3.1	267	
T. A.	6720	2910	1.2	619	
J. B.	11,000	10,300	7.3	175	
$\overline{X}$	9340	5680	1.9†	‡	
± SE	945	1800	—	—	
50 × 10⁶ dose					
M. P.	38,000	32,800	3.0	152	—
E. F.	43,400	35,100	6.4	142	610:1
T. A.	32,900	26,900	1.7	186	1100:1
J. B.	38,600	37,600	11.2	133	550:1
$\overline{X}$	38,200	33,100	3.4†	153	
± SE	2150	2300	—	12	

*Concentration at end of 10-min infusion.
†Harmonic mean $t_{1/2}$.
‡Mean not determined (see text).

specific for separate epitopes of rIFN-αA.[3] After binding of the sandwich to O-phenylenediazimine, the complex was measured photometrically to determine rIFN-αA serum concentrations. The reference standard had specific activity of 1.7 × 10⁸ U/mg protein as determined against the National Institutes of Health interferon standard. Assay sensitivity in serum was 15 pg/ml.

RESULTS

Mean serum rIFN-αA concentrations after single i[n]travenous doses of 18 and 50 × 10⁶ U are listed [in] Table I. Data from a representative individual a[re] plotted in Fig. 1.

Maximum serum concentrations (C_{max}) ranged fro[m] 6720 to 11,000 pg/ml ($\overline{X}$ = 9340 pg/ml) and fro[m] 32,900 to 43,400 pg/ml ($\overline{X}$ = 38,200 pg/ml) after

and 50×10^6 U rIFN-αA (Table II). C_{max} was reached at the end of infusion and was followed by a 3000% decrease in concentrations within 4 hr after the end of the infusion. This rapid distribution was followed by an apparent terminal elimination phase, with t½s ranging from 1.2 to 1.3 hr (harmonic mean = 1.9 hr) and from 1.7 to 11.2 hr (harmonic mean = 3.4 hr) after 18 and 50×10^6 U rIFN-αA (Table II). Total body clearance ranged from 133 to 186 ml/min ($\overline{X}$ = 153 ml/min) after the 50×10^6 U dose (Table II). Two of the four clearance values after the 18×10^6 U dose were extremely high (>600 ml/min). Inspection of the serum concentration-time data for these two subjects suggested that the disposition profile may not have been adequately characterized, since serum concentrations approached the sensitivity of the assay before reaching the elimination phase. Therefore, the AUC for the two subjects with high clearance values were 300% to 500% less than expected. Since clearance is the quotient of dose over AUC, a decrease in AUC would produce a corresponding increase in clearance (as observed in these two subjects). Overall, the disposition and kinetic profile of rIFN-αA in these subjects is consistent with data involving patients with cancer* and normal subjects.[11]

There were no measurable concentrations of rIFN-αA in the CSF of subjects receiving the 18×10^6 U dose (Table I). Three of the four subjects who received the 50×10^6 U dose had measurable concentrations of rIFN-αA ranging from 17 to 70 pg/ml that appeared no earlier than 1 hr after starting the infusion and in two cases were measurable throughout 24 hr. The rIFN-αA concentration in serum/CSF ratio ranged from 550:1 to 1100:1 (Table II).

The spectrum of acute side effects in most subjects was of the order of those reported by others.[11] Fever, loss of appetite, fatigue, headache, and muscle ache were the most frequent side effects. Two subjects had severe back and leg pain that was relieved with analgesics.

DISCUSSION

Our finding that rIFN-αA does not readily cross the blood-brain barrier in man parallels the result recently reported in the Rhesus monkey.[5] The same interferon was used in both studies. In an earlier study with partially purified interferon, penetration of interferon into the CSF was better, but this may be related to species

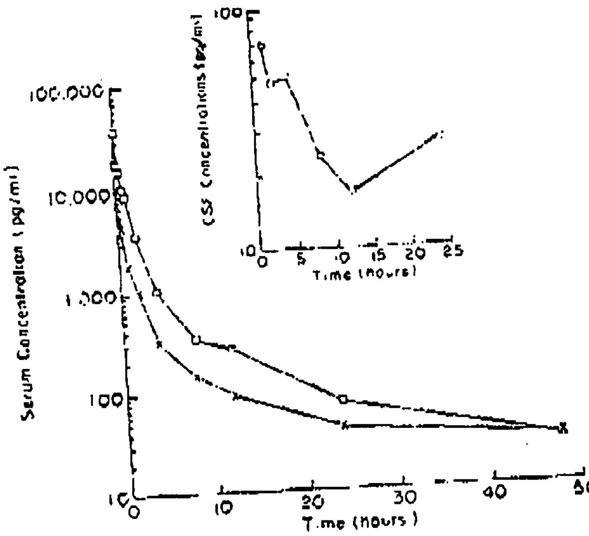

Fig. 1 Serum rIFN-αA concentrations after a single 18×10^6 U (X) or 50×10^6 U (O) dose in a 10-min infusion in subject J. B. The *inset* represents CSF concentrations of rIFN-αA after the 50×10^6 U dose.

differences, use of a different interferon, or use of a biologic assay to measure interferon.

The finding that rIFN-αA does not readily cross the blood-brain barrier must be interpreted with caution. Although the CSF level of rIFN-αA provides general information about the permeability of the blood-brain barrier, it does not permit prediction of the concentration of rIFN-αA or rIFN-αA fragments that reach specific populations of nerve or glial cells. The blood-brain barrier is particularly permeable at three sites: the infundibular recess, the median eminence, and the area postrema.[1] Accordingly, systemically administered rIFN-αA might reach high concentrations at some brain sites while failing to do so at others. In animals and man, high CSF levels of rIFN-αA can be achieved by injection of interferon directly into the ventricular CSF, and interferon injected by this route circulates throughout the CSF pathway.[3,14] The side effects noted with intraventricular and systemic administration are of the same order.

Recent reports describe the occurrence of disorientation, confusion, somnolence, and hallucinations in patients receiving a continuous infusion of 100 to 200×10^6 U rIFN-αA daily for 4 to 5 days for cancer.[7,12] These side effects are accompanied by electroencephalographic and biochemical abnormalities, but they do

*Wills RJ: Unpublished observations, 1983.

not appear to correlate with the presence of rIFN-αA in the CSF. Interferon (approximately 100 U/ml) can be detected in the CSF of some but not all patients who manifest central nervous system side effects. The basis for these effects is not known. Calvert and Gresser[2] have reported that human leukocyte interferon enhanced the spontaneous activity and evoked responses of neurons cultured from explants of cat cerebral and cerebellar cortex. A long-lasting effect on firing discharge was noted when leukocyte interferon was injected microiontophoretically into rat cortical and thalamic neurons, although the effect was more pronounced in the cortex than in the thalamus.[7] These experiments suggest interferon can directly affect neuronal excitability. With high-dose systemic administration, interferon may reach high concentrations in the pons and hypothalamus, where the blood-brain barrier is permeable.[11] Interruption of brainstem functions, subserved by the reticular activating system and other structures, could account for most of the side effects associated with high-dose rIFN-αA therapy. We cannot exclude the possibility that metabolic encephalopathy or some other indirect effect of rIFN-αA is responsible for the nervous system side effects currently attributed to rIFN-αA.

Our finding in man that systemically administered rIFN-αA does not readily cross the blood-brain barrier deserves emphasis in the design and interpretation of treatment trials of neurologic diseases with rIFN-αA, and ultimately our results must be reconciled with the occurrence of central nervous system toxicity in patients treated with rIFN-αA.

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A DRUG NAME: INTERFERON ALFA

SYNONYM(S): IFN, Interferon-Alpha

COMMON TRADE NAME(S): **Roferon® -A (alfa 2a) (Hoffman-La Roche)**
Intron A® (alfa 2b) (Schering)

B MECHANISM OF ACTION AND PHARMACOKINETICS

Interferons are a group of naturally occurring proteins that have a broad range of activities that are antiviral, antiproliferative, cytostatic, immunomodulatory, differentiating, and inhibitory of cellular genes, including oncogenes. Interferons can act directly on tumour cells as well as effector cells such as NK cells, T cells, and macrophages.

Oral Absorption	No, degraded by enzymes	
Distribution	Large glycoprotein with poor interstitial penetration. 80% absorbed after i.m. or sc injection. Pharmacokinetics is linear.	
	Cross blood brain barrier?	Trace
	PPB	No information found
Metabolism	Catabolized by proteolysis in renal tubular cells during reabsorption	
	Active metabolite(s)	No
	Inactive metabolite(s)	Yes
Excretion	Disposition described by two-compartment model	
	Urine	No
	t ½	3.7-8.5 hours

C INDICATIONS AND STATUS

- * Basal cell carcinoma
- * chronic active hepatitis (B or C)
- * Chronic myelogenous leukemia
- * Condylomata accuminata
- * Cutaneous T cell lymphoma
- * Hairy cell leukemia
- * Hemangiomas of infancy and childhood
- * Kaposi's sarcoma (patients with AIDS)
- * Malignant melanoma
- * Multiple myeloma
- * Non-Hodgkin's lymphoma
- * Renal cell carcinoma
- * Malignant Melanoma

Other uses include:

Bladder cancer

* Health Canada approved indication

Interferons

Produced by B and T lympocytes, macrophages and fibroblasts in response to viruses and cytokines

Family of inducible proteins of at least 3 types

- Alpha-interferon -- smallest at 20,000 Daltons
- Beta-interferon -- ~28,000 Daltons

Cytokines produced by T lymphocytes in response to antigens, including many infectious agents

- Gamma-interferon -- ~70,000 Daltons

Mechanism of action

Interferons relatively species specific

MOA may differ with interferon

Modes include inhibition of --

- viral penetration or uncoating
- synthesis or methylation of mRNA
- translation of viral proteins
- viral assembly and release
- For some viruses, no inhibition of viral RNA or protein synthesis (GG8th90)
- Inducing host to produce enzymes that inhibit translation of viral RNA into proteins
- Three enzymes produced, but not active!
  - a 2'-5' oligoadenylate (2-5A) synthetase
  - a protein kinase
  - an endonuclease

- When virus invades and new viral RNA is synthesized --
  - New viral RNA activates the "synthetase" and "kinase"
  - Activated "synthetase" polymeryses ATP into 2'-5'-oligonucleotides
  - New oligonucleutides activate the "endonuclease" which degrades viral RNA
  - Activated "kinase" phosphorylates alpha subunit of eukaryotic initiation factor 2
  - Phosphorylated factor 2 inhibits viral protein synthesis
  - Basis for specificity of these enzymes for viral macromolecules not known

Unexpected actions of interferons

- enhance cytotoxic activities of lymphocytes
- inhibit cell proliferation
- inhibit expression of cell surface antigens,
- inhibit phagocytic and tumoricidal activities of macrophages

Pharmacokinetics

- Given IV or IM
- Half-life -- 2-4 hr
- Not cross blood-brain barrier

Adverse effects

- Alpha-Interferon (Alpha-IFN) given IM or IV
  influenza-like signs
  - fever, headache, malaise, myalgia
  - Alpha-IFN may be cause of these signs in illness
  Bone marrow suppression -- common
  - thrombocytopenia
  - granulocytopenia
- Neurotoxicity
  See references for more signs

Uses

- Approved by FDA: Interferon alfa-2a ROFERON-AR and Interferon alfa-2b Intron AR
  hairy-cell leukemia,
  AIDS-related Kaposi's sarcoma
  genital warts
  hepatitis B

Interferon inducers

- Generally not found to be safe and effective
- Agents tried include
  certain microorganisms (e.g., viruses, Rickettsia, Mycoplasma, coliform bacteria),
  microbial extracts
  certain dyes (e.g., methylene blue, acridince orange),
  synthetic polymers.

back to antivirals

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